

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
22 March 2001 (22.03.2001)

PCT

(10) International Publication Number  
WO 01/19378 A2

(51) International Patent Classification<sup>7</sup>: A61K 35/00 (74) Agent: WITTE, Hubert; 124, Grenzacherstrasse, CH-4070 Basle (CH).

(21) International Application Number: PCT/EP00/08857

(22) International Filing Date: 11 September 2000 (11.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 99118179.3 13 September 1999 (13.09.1999) EP

(71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; 124, Grenzacherstrasse, CH-4070 Basle (CH).

(72) Inventors: DE SMIDT, Passchier, Christiaan; Benjamin de Tudela, 25-2B, E-31008 Pamplona (ES). HADVARY, Paul; Neumattenweg 8, CH-4105 Biel-Benken (CH). LENGSFELD, Hans; Marschalkenstrasse 35, CH-4054 Basle (CH). SCHMID, Marcel; 2, Rebgasse, CH-4153 Reinach (CH). SMALL, David, MacFarland; 87 Harbourside Road, Quincy, MA 02171 (US). STEFFEN, Hans; 36, Fischmarkt, CH-4410 Liestal (CH). TARDIO, Joseph; 14, rue Petite Camargue, F-68300 St. Louis (FR).

(81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— Without international search report and to be republished upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

O 01/19378 A2

(54) Title: SOLID LIPID FORMULATIONS

(57) Abstract: The present invention refers to a pharmaceutical composition comprising at least one inhibitor of lipases and at least

Solid lipid formulations

The present invention relates to pharmaceutical compositions comprising at least one lipase inhibitor.

Examples of such lipase inhibitors are lipstatin and orlistat. The latter is also known

5 as tetrahydrolipstatin or THL and is derived from a natural product excreted by *Streptomyces toxytricini*. This class of compounds was found to exhibit *in vitro* as well as *in vivo* activity against various lipases, such as lingual lipase, pancreatic lipase, gastric lipase, and carboxylester lipase. Its use for the control or prevention of obesity and hyperlipidemia is described, for instance, in US Patent 4,598,089.

10 Orlistat is currently administered at doses of 120 mg per meal and dosing is independent of the body mass of the human subject. Orlistat acts locally in the gastrointestinal (GI) tract and prevents lipase from digesting triglycerides and subsequently inhibits the formation of absorbable lipid degradation products. For this reason, systemic availability of the lipase inhibitors is not required and, instead, local residence in the gastrointestinal tract is preferred.

15

Lipase inhibitor compositions currently administered inhibit around 30% of fat absorption after consumption of a mixed meal; an increase of the lipase inhibitors concentration in the pharmaceutical composition does not increase its clinical efficacy and/or potency while the intensity of local side effects increases.

20 Anal leakage of oil (oily spotting) is an adverse effect which is occasionally observed in patients treated with lipase inhibitors. This phenomenon reflects physical separation of some liquid unabsorbed dietary fat from the bulk of solids in the lower large intestine.

- 2 -

The problem at the root of the present invention is therefore to provide lipase inhibitor compositions which are able to improve the clinical efficacy and/or potency of the inhibitor itself, and to minimize or suppress the above mentioned disadvantages.

The problem is solved, according to the present invention, by a pharmaceutical composition comprising at least one inhibitor of lipases and at least one fatty acid ester of polyols, characterized in that the fatty acid ester has a melting point above the body temperature, i.e. >37°C, and the polyols are chosen from the group consisting of glycerol, sugars, sugar derivatives and mixtures thereof.

It has surprisingly been found that administering a lipase inhibitor in a composition comprising at least one of the above fatty acid esters clearly improves the efficacy and potency of the lipase inhibitor itself. Furthermore, the inter-subject variability in efficacy and/or potency is reduced, as well as the frequency and intensity of side effects.

The pharmaceutical compositions according to the present invention have been found to exhibit very favorable effects when applied orally during meal intake in humans. Surprisingly, an increased efficacy and potency compared to the already known compositions was observed. This was unexpected as the compositions according to the invention are solid within the body and should therefore be poorly dispersible among the dietary oil particles in the stomach.

Furthermore, the compositions according to the present invention reduce unpleasant side effects in the single meal test compared to the already known compositions, despite the greater amount of fat which remains unabsorbed. During the single meal studies with human subjects, it was observed that the stools obtained after intake of compositions according to the present invention show less separation of oil from the main stool mass as compared to the conventional formulations. This was unexpected, as equal or higher amounts of fat were present in the collected stools.

According to the present invention, the terms "inhibitor of lipases" and "lipase inhibitor" refers to compounds which are capable of inhibiting the action of lipases, for example gastric and pancreatic lipases. For example orlistat and lipstatin as described in U.S. Patent No. 4,598,089 are potent inhibitor of lipases. Lipstatin is a natural product of microbial origin, and orlistat is the result of a hydrogenation of lipstatin. Other lipase inhibitors include a class of compound commonly referred to as pандlicins, analogues of orlistat (Mutoh et al, 1994). The term "lipase inhibitor" refers also to polymer bound lipase inhibitors for example described in International Patent Application WO99/34786 (Geltex Pharmaceuticals Inc.). These polymers are characterised in that they have been functionalized with groups that inhibit lipases. The term "lipase inhibitor" also

comprises pharmaceutically acceptable salts of these compounds. The term "lipase inhibitor" preferably refers to orlistat.

Orlistat is a known compound useful for the control or prevention of obesity and hyperlipidemia. See, U.S. Patent No. 4,598,089, issued July 1, 1986, which also discloses 5 processes for making orlistat and U.S. Patent No. 6,004,996, which discloses appropriate pharmaceutical compositions. Further suitable pharmaceutical compositions are described for example in International Patent Applications WO 00/09122 and WO 00/09123. Additional processes for the preparation of orlistat are disclosed in European Patent Applications Publication Nos. 185,359, 189,577, 443,449, and 524,495.

10 Orlistat is preferably orally administered from 60 to 720 mg per day in divided doses two to three times per day. Preferred is wherein from 180 to 360 mg, most preferably 360 mg per day of a lipase inhibitor is administered to a subject, preferably in divided doses two or, particularly, three times per day. The subject is preferably an obese or overweight human, i.e. a human with a body mass index of 25 or greater. Generally, it is preferred that 15 the lipase inhibitor be administered during ingestion of a meal containing fat. Generally, for administering a lipase inhibitor as defined above it is preferred that treatment be administered to a human who has a strong family history of obesity and has obtained a body mass index of 25 or greater.

Accordingly, the present invention refers to a composition comprising at least one 20 inhibitor of lipases and at least one fatty acid ester of polyols, characterized in that the fatty acid ester has a melting point above the body temperature and the polyols are chosen from the group consisting of glycerol, sugars, sugar derivatives and mixtures thereof.

The polyols can be chosen, independently from each other, from the group 25 consisting of glycerol, sugars, sugar derivatives and mixtures. This group especially comprises sucrose, glycerol, and sugar alcohols, and most preferably glycerol, i.e. most preferably glyceride esters are used in the compositions according to the present invention.

The term "sugar alcohols" refer to compounds comprising mono-, oligo- and polysaccharides and their reduction products, e.g. mannitol.

The term "glyceride ester" refers to an ester of glycerol. According to the present 30 invention, an ester may contain one to three, preferably one or three C12 to C20 fatty acid(s) moieties per glycerol moiety or may be a phospholipid, preferably a lecithin or mixtures thereof. For example, the glyceride esters can be chosen from the group consisting of one or more triglycerides, one or more monoglycerides, one or more

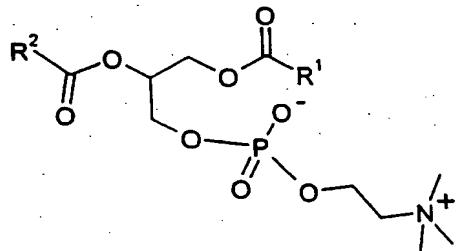
- 4 -

phospholipids and mixtures thereof. Preferably, the fatty acid moieties in the fatty acid ester of the polyols have, independently from each other, twelve or more carbon atoms, preferably twelve to twenty carbon atoms. Most preferably, the fatty acid moieties in the fatty acid ester of the polyols have twelve to twenty carbon atoms and are saturated.

5 In a preferred embodiment of the present invention suitable triglycerides are trilaurin, trimyristin, tripalmitin and tristearin and mixtures thereof. The most preferred triglycerides are trimyristin and trilaurin.

The monoglycerides can be chosen from the group consisting of monocaprin, monolaurin, monomyristin and monopalmitin and mixtures thereof.

10 In a preferred embodiment of the present invention, the phospholipid is preferably a lecithin, e.g. a non-, partially or fully hydrogenated lecithin and mixtures thereof. The term "lecithin" in the context of this invention refers to esters formed of glycerol, two fatty acids, and a phosphorylcholine moiety. A lecithin has the following structure:



15 wherein R<sup>1</sup>-COO- and R<sup>2</sup>-COO- are moieties derived from fatty acids as defined above.

The phospholipids, e.g. lecithins, may be chosen from the group consisting of natural lecithin, synthetic lecithin, sojalecithin, egglecithin, synthetic dipalmitoyllecithin, partially or fully hydrogenated lecithin and mixtures thereof.

The fatty acid esters of polyols are known in the art and are commercially available.

20 Preferably, the glyceride ester is present in an amount varying between 0.5 and 90 % of the total weight of the composition.

Advantageously, the pharmaceutical compositions of the present invention further comprise at least one pharmaceutically acceptable excipient. The additional excipient may be useful for enhancing the dispersion and distribution in the stomach. The excipient may

25 be chosen from the group consisting of disintegrants, effervescents and mixtures thereof. Further excipients such as carbohydrates, starch and/or its derivatives, maltodextrines, cellulose, cellulose derivatives, sugars, fillers, antioxidants, anionic and nonionic

poly(oxyethylene)alkyl esters, poly(oxyethylene)alkyl ethers and mixtures thereof can also be added. Examples of additional excipients are glucose, lactose, sorbitol, maltodextrin, talcum, magnesium stearate, mannitol, sodium bicarbonate, crospovidone, glycofurool, tartaric acid and mixtures thereof

5 The invention is useful with any inhibitor of lipases, but is especially useful for inhibitors of the gastric and pancreatic lipase and, in particular, for the active compound orlistat.

According to the present invention, the lipase inhibitor is present in an amount varying from 1 to 50%, preferably from 5 to 30%, of the total weight of the composition.

10 In a preferred embodiment of the present invention the pharmaceutical composition as described above may comprise

- a) 1 to 50% of the total weight of the composition is a lipase inhibitor;
- b) 0.5 to 90% of the total weight of the composition is at least one fatty acid ester of polyols; and optionally

15 the composition comprises one or more pharmaceutically acceptable excipient(s).

The compositions according to the present invention can be administered using conventional dosage forms such as hydroxypropylmethylcellulose (HPMC) capsules, hard gelatin capsules, starch capsules, tablets, chewable tablets and capsules, powders, pellets, granules, etc.

20 The present invention relates also to a process for preparing pharmaceutical compositions as described above, which process comprises mixing at least one inhibitor of lipases with at least one fatty acid ester of polyols, in the solid or molten state, wherein the fatty acid ester of polyols has a melting point above the body temperature and the polyols are chosen from the group consisting of glycerol, sugars, sugar derivatives and mixtures 25 thereof.

A further aspect of the present invention is to provide a method for controlling or preventing obesity comprising the step of administering to a patient a pharmaceutical composition as described above.

30 The invention also relates to the use a composition as defined above for the preparation of a medicament for the prevention and treatment of obesity.

The invention will be now illustrated in details by the following examples.

- 6 -

The efficacies on fat excretion of orlistat formulations according to examples 1-10 and of Xenical® as a reference are reported in table 1.

EXAMPLESExample 1

10 g of melted trimyristin (Dynasan 114, Hüls AG) were mixed with 20 g orlistat 5 during about 30 minutes at a temperature of 57-63°C. 20 g glucose were added to the so obtained co-melt and mixed until solidification at room temperature. The so obtained cake was left for an hour at room temperature, ground by means of a dry mixer and subsequently sieved through meshes of 1.6 mm. The resulting particles were heated at 39°C for 4.5h under inert atmosphere, cryo-milled with dry ice and subsequently mixed with 10 lactose (lactose : resulting particle = 100 : 15 w:w). The so obtained mixture was finally pressed into chewable tablets having a diameter of 16 mm, a weight of 1.15 g and containing each 60 mg orlistat, 30 mg trimyristin, 60 mg glucose and 1000 mg lactose.

The above chewable tablets were applied to human volunteers during a single meal test. Human subjects consumed a meal consisting of 130 g hamburger meat, 10 g butter 15 and 100 g French fries (fried in peanut oil) and containing overall about 35 g fat. Stools were collected from day -1 (a day before eating the single meal) until day 5 after the test meal. The first and the last stools were employed to assess background fat excretion. Stools were stored frozen and extracted for total lipid according to Bligh and Dyer (Bligh, E.G., and Dyer, W.J., *Can. J. Biochem. Physiol.*, 37, (1959), 911). Background excretion of 20 lipids was subtracted to obtain the amount of fat excreted due to the orlistat treatment. The excreted fat was quantified by gravimetry and expressed as percentage of the fat content of the test meal.

Example 2

100 g of trimyristin (Dynasan 114, Hüls AG) were melted at 65°C in a suitable high 25 shear mixer vessel. 200 g orlistat were given in the vessel and molten by mixing softly (mixture = comelt). The molten phase was mixed for 2 minutes. While stirring, 1800 g maltodextrin DE 21 (ratio comelt :maltodextrin = 1:6 w:w) were added in two portions and mixed until solidification at room temperature and a flowing granulate was obtained. The granulate was sieved through meshes of 0.85 mm. Separately, 4950 g sorbitol were 30 sieved through meshes of 0.85 mm and mixed with the co-melted granulate for 3 minutes. Additionally, the outer phase (375 g talcum and 75 g magnesium stearate) were hand sieved through meshes of 0.5 mm and mixed with the granulate for 3 minutes. The so obtained mixture was finally pressed into chewable tablets having a diameter of 20 mm, a weight of 1.5 g and containing each 40 mg orlistat, 20 mg trimyristin, 360 mg

- 8 -

The above chewable tablets were applied to human volunteers according to the method described in Example 1.

Example 3

1.25 g HPMC (Pharmacoat 603, Shin-Etsu Chemical Co) were dissolved in 39.5 g 5 water at about 75 °C. The solution was cooled to room temperature (25°C) and a dispersion was obtained by adding thereto 5 g mannitol, 2.5 g sodium bicarbonate and 1 g Crospovidone. 0.75 g Kryosomes 1703H (hydrogenated lecithin, Lipoid AG) were dispersed in 7.5 g water with a homogenizer (Polytron) for 30 seconds and successively 10 mixed with the above dispersion. The obtained aqueous system was used to make an emulsion by emulsifying, with a Polytron for 1.5 minutes at 65 °C, 4.5 g of a melted oily mixture obtained by melting 3.15 g trimyristin (Dynasan 114, Hüls AG) and 6.3 g orlistat at 65 °C. This emulsion was frozen at -80 °C in a rotating 250 ml round flask in a dry ice-ethanol mixture and was then lyophilized. The lyophilisate was then milled at room 15 temperature and 3 g thereof were mixed and sieved through meshes of 0.5 mm. 1.3 g of the mixture was pressed to a chewable tablet having a diameter of 16 mm diameter, a weight of 1.3 g and containing each 60 mg orlistat, 30 mg trimyristin, 15 mg Kryosome, 25 mg HPMC, 20 mg Crospovidone, 100 mg mannitol, 50 mg sodium bicarbonate and 1000 mg lactose.

The above chewable tablets were applied to human volunteers according to the 20 method described in Example 1.

Example 4

30 g orlistat and 15 g trimyristin (Dynasan 114, Hüls AG) were spread through meshes of 0.9 mm and mixed for 10 minutes. The mixture was again sieved through meshes of 0.9 mm and mixed for 10 minutes. The so obtained mixture was coarse milled 25 (in portions) for 0.5 minutes in a dry mixer by adding a triple amount of dry ice. This cold mixture was then cryo-milled with a pin mill to get fine particles. The resulting particles were dried during 15 minutes under high vacuum and subsequently mixed with 2/3 (w/w) part of glucose. 15 g of this dry mix was mixed with 100 g lactose for 10 minutes and then sieved through meshes of 0.5 mm. The so obtained mix-milled granulate was finally 30 pressed into chewable tablets having a diameter of 16 mm, a weight of 1.15 g and containing each 60 mg orlistat, 30 mg trimyristin, 60 mg glucose and 1000 mg lactose.

The above chewable tablets were applied to human volunteers according to the method described in Example 1.

Example 5

1.2 g orlistat and 1.8 g glucose were sieved through meshes of 0.9 mm and mixed for 2 minutes. Afterwards 4.0 g Kryosome 1702 (soyalecithin : sucrose = 1:2 w:w; Lipoid AG) were also sieved through meshes of 0.9 mm and mixed with the first mixture for 2 minutes.

5 The combined mixture was then cryo-milled with an air-jet mill using dry ice for cooling. The resulting particles were dried for 15 minutes under high vacuum. 3.5 g of the dried particles were mixed with 10 g lactose for 15 minutes. The so obtained powder mixture was finally pressed into chewable tablets having a diameter of 16 mm, a weight of 1.35 g and containing each 60 mg orlistat, 90 mg glucose, 200 mg Kryosome and 1000 mg lactose.

10 The above chewable tablets were applied to human volunteers according to the method described in Example 1.

Example 6

4.24 g soyalecithin and 4.24 g orlistat were subsequently dissolved in 31.52 g glycofurool 75 (Roche). Empty hard gelatin capsules were sealed with a 25 % gelatin solution in water and were allowed to dry. The sealed hard gelatin capsules were punched and subsequently filled with 565 mg of the orlistat/lecithin/glycofurool-solution. The holes were closed with the above gelatin solution and the closed capsule was allowed to dry for at least 15 minutes. Every capsule contained 60 mg orlistat, 60 mg soyalecithin and 445 mg glycofurool.

20 Capsules prepared in this way were applied to human volunteers according to the method described in Example 1.

Example 7

10 g of melted trimyristin (Dynasan 114, Hüls AG) were mixed with 20 g orlistat during about 30 minutes at a temperature of 57-63°C. 20 g glucose were added to the so obtained co-melt and mixed until solidification at room temperature, ground by means of a dry mixer and subsequently sieved through meshes of 1.6 mm. 48 g of resulted particles were kept at 39°C in a closed vial under inert atmosphere for 4.5h, cryo-milled with dry ice on a pin mill. 15 g of the resulted particles were subsequently mixed with 10 g Kryosome 1702 (Lipoid AG) and 100 g lactose for 30 minutes. The mixture was sieved through meshes of 0.5 mm and pressed into chewable tablets, having a diameter of 16 mm, a weight of 1.25 g and containing each 60 mg orlistat, 30 mg trimyristin, 60 mg glucose, 100 mg Kryosome and 1000 mg lactose.

- 10 -

The above chewable tablets were applied to human volunteers according to the method described in Example 1.

Example 8

0.75 g of co-melted and cryo-milled material (orlistat-trimyristin-glucose 2:1:2)

5 from Example 7 and 0.5 g Kryosome 1702 were sieved through meshes of 0.5 mm and mixed for 10 minutes. 3.0 g sodium bicarbonate and 1.5 g tartaric acid were milled at room temperature in a laboratory blade mill, sieved through meshes of 0.5 mm and mixed for 10 minutes. 2.7 g of this effervescent mixture was added to the first mixture and mixed again for 10 minutes. 0.395 g of this mixture were filled into HPMC capsules of size 0,

10 containing 30 mg orlistat, 15 mg trimyristin, 30 mg glucose, 50 mg Kryosome, 180 mg sodium bicarbonate and 90 mg tartaric acid.

The above capsules were applied to human volunteers according to the method described in Example 1.

Example 9

15 20 g orlistat and 10 g trilaurin (Dynasan 112, Hüls AG) were sieved through meshes of 0.5 mm and mixed. This mixture was cryo-milled in a pin mill together with dry ice and subsequently dried under vacuum for 15 minutes. 10 g of this mixture was blended with 15 g glucose. 3g of this blend and 2 g of Kryosomes 1702 (Lipoid AG) were cryo-milled together with dry ice in a laboratory blade-mill and dried overnight in a dessicator under

20 vacuum. 1.25 g of the resulting powder were pressed to a chewable tablet having a diameter of 16 mm, a weight of 1.25 g and containing each 60 mg orlistat, 30 mg trilaurin, 60 mg glucose, 100 mg kryosome and 1000 mg lactose.

The above chewable tablets were applied to human volunteers according to the method described in Example 1.

25

Example 10

16 g monolaurin (Rylo MG12, Danisco Ingredient AG) and 4 g monocaprin emulsifier TS-PH003 (Danisco Ingredient AG) were comelted at about 70 °C, cooled to room temperature (25°C) and thereby completely solidified. After one day the film was scraped off the wall with a spatula, coarse milled, in portions, in a dry mixer at low

30 temperature by adding dry ice (three times the volume of the to milled material) for about half a minute and then fine cryo-milled in a pin mill and vacuum dried for 15 minutes. 15 g of this mixture and 15 g orlistat were blended. 50 g dry ice were added and the mixture is coarse milled in portions each for half a minute. After vacuum drying the resulting powder

was sieved through meshes of 0.9mm and fine cryo milled in a pin mill to produce a fine orlistat-monocaprin-monolaurin (50-10-40) powdermix. 2.4 g of a comilled mixture between 2.16 g tartaric acid and 4.56 g sodiumbicarbonate was added to 5.6 g of the above powdermix and 2 g anhydrous lactose, mixed for 5 minutes and sieved through meshes of 5 0.5 mm and mixed again. 500 mg of the resulting powder were filled in hard gelatin capsules containing 60 mg orlistat, 48 mg monolaurin, 12 mg monocaprin, 100 mg lactose, 190 mg sodium bicarbonate and 90 mg tartaric acid.

The above capsules were applied to human volunteers according to the method described in Example 1.

10

Table 1: In vivo results

Example	Orlistat dose (mg)	Excreted fat <sup>(1)</sup>	n <sup>(2)</sup>	Free oil in stool samples <sup>(3)</sup>
Reference	120 mg (Xenical®)	41.8 ± 11.5	18	9/18
1	60 mg	48.1 ± 3.9	3	1/3
2	40 mg	37.6 ± 17.1	5	0/5
3	60 mg	50.2 ± 13.4	3	1/3
4	60 mg	43.1 ± 15.6	5	0/5
5	60 mg	64.8 ± 14.3	5	0/5
6	60 mg	47.2 ± 12.0	5	n.d.
7	60 mg	82.0 ± 5.5	6	0/6
8	30 mg	40.6 ± 10.6	5	0/5
9	60 mg	60.6 ± 13.3	5	2/5
10	60 mg	54.2 ± 10.9	5	1/5

<sup>(1)</sup> excreted fat as percentage of fat intake.

<sup>(2)</sup> number of volunteers subjected to the experiments

<sup>(3)</sup> number of stool samples containing free oil/number of volunteers

- 12 -

As shown in Table 1, the efficacy and/or potency of the compositions according to the present invention is much higher than that of conventional formulations. Compositions according to the invention containing just the half or even a quarter of the lipase inhibitor of the known composition are similarly or even much more efficacious 5 and/or potent. For the same lipase inhibition degree, it is now possible to strongly decrease the amount of active compound in the composition, thus minimizing undesired side effects.

Table 1 shows also the number of stool samples containing free oil for each of the 10 above compositions. Stool samples obtained after intake of compositions according to the present invention show just occasional separation of oil from the main stool mass or no separation at all. The compositions according to the present invention enable therefore to minimize or completely suppress anal leakage of oil which is one of the most undesired side effect of the prior art compositions.

CLAIMS

1. A pharmaceutical composition comprising at least one inhibitor of lipases and at least one fatty acid ester of polyols, characterized in that the fatty acid ester has a melting point above the body temperature and the polyols are chosen from the group consisting of glycerol, sugars, sugar derivatives and mixtures thereof.  
5
2. The pharmaceutical composition according to claim 1, wherein the polyols are chosen, independently from each other, from the group consisting of sucrose, glycerol, and sugar alcohols.
3. The pharmaceutical composition according to claim 1 or 2, wherein the polyol is glycerol.  
10
4. The pharmaceutical composition according to any of claims 1 to 3, wherein the fatty acid ester is a glyceride ester and is chosen from the group consisting of one or more triglycerides, one or more monoglycerides, one or more phospholipids and mixtures thereof.
- 15 5. The pharmaceutical composition according to any of claims 1 to 4, wherein the fatty acid moieties in the fatty acid ester of the polyol have, independently from each other, twelve or more carbon atoms and the fatty acid moieties in the fatty acid ester of the polyol are saturated.
- 20 6. The pharmaceutical composition according to claim 5, wherein the fatty acid moieties in the fatty acid ester of the polyol have, independently from each other, twelve to twenty carbon atoms.
7. The pharmaceutical composition according to any of claims 4 to 6, wherein the triglycerides are chosen from the group consisting of trilaurin, trimyristin, tripalmitin, tristearin and mixtures thereof.
- 25 8. The pharmaceutical composition according to claim 7, wherein the triglyceride is trimyristin or trilaurin or mixtures thereof.
9. The pharmaceutical composition according to any of claims 4 to 6, wherein the monoglycerides are chosen from the group consisting of monocaprin, monolaurin, monomyristin, monopalmitin and mixtures thereof.
- 30 10. The pharmaceutical composition according to any of claims 4 to 6, wherein the phospholipid is a lecithin.

- 14 -

11. The pharmaceutical composition according to claim 10, wherein the phospholipid is a non-, partially or fully hydrogenated lecithin and mixtures thereof.
12. The pharmaceutical composition according to claim 10 or 11, wherein the phospholipids are chosen from the group consisting of natural lecithin, synthetic lecithin, sojalecithin, egglecithin, synthetic dipalmitoyllecithin, partially or fully hydrogenated lecithin and mixtures thereof.  
5
13. The pharmaceutical composition according to any of claims 1 to 12, wherein the fatty acid ester of polyols is present in an amount varying between 0.5 % and 90 % of the total weight of the composition.
- 10 14. The pharmaceutical composition according to any of claims 1 to 13, further comprising at least one pharmaceutically acceptable excipient.
- 15 15. The pharmaceutical composition according to claim 14, wherein the excipient is selected from the group consisting of carbohydrates, starch and/or its derivatives, maltodextrines, cellulose, cellulose derivatives, sugars, fillers, disintegrants, effervescents, antioxidants, anionic surfactants, nonionic surfactants and mixtures thereof.
16. The pharmaceutical composition according to claim 15, wherein the surfactant is selected from the group consisting of sodium dodecylsulfate, fatty acid salts, polyoxyethylene alkyl esters and polyoxyethylene alkyl ethers and mixtures thereof.
- 20 17. The pharmaceutical composition according to any of claims 14 to 16, comprising an excipient selected from the group consisting of glucose, lactose, sorbitol, maltodextrin, talcum, magnesium stearate, mannitol, sodium bicarbonate, Crospovidone, glycofurool, tartaric acid and mixtures thereof.
- 25 18. The pharmaceutical composition according to any of claims 1 to 17, wherein the inhibitor of lipases is an inhibitor of gastrointestinal lipases.
19. The pharmaceutical composition according to claim 18, wherein the inhibitor of gastrointestinal lipases is orlistat.
- 30 20. The pharmaceutical composition according to any of claims 1 to 19, wherein the lipase inhibitor is present in an amount varying from 1 to 50% of the total weight of the composition.
21. The pharmaceutical composition according to claim 20, wherein the lipase inhibitor is present in an amount varying from 5 to 30% of the total weight of the composition.

- 15 -

22. The pharmaceutical composition according to any of claims 1 to 21, wherein
  - a) 1 to 50% of the total weight of the composition is at least one lipase inhibitor;
  - b) 0.5 to 90% of the total weight of the composition is at least one fatty acid ester of polyols; and optionally
  - 5 c) the composition comprises one or more pharmaceutically acceptable excipient(s).
23. A process for preparing a pharmaceutical composition according to any one of claim 1 to 22, comprising mixing at least one inhibitor of lipases with at least one fatty acid ester of polyols, wherein the fatty acid ester of polyols has a melting point above the body temperature and the polyols are chosen from the group consisting of glycerol, sugars, sugar derivatives and mixtures thereof.  
10
24. Use of a pharmaceutical composition as defined in any one of claim 1 to 22 for controlling or preventing obesity.
25. A method for controlling or preventing obesity comprising the step of administering to  
15 a patient a pharmaceutical composition as defined in any one of claims 1 to 22.
26. Use of a composition as defined in any of claims 1 to 22 for the preparation of a medicament for the prevention and treatment of obesity.
27. The invention as hereinbefore described.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
22 March 2001 (22.03.2001)

PCT

(10) International Publication Number  
WO 01/19378 A3

(51) International Patent Classification<sup>7</sup>: A61K 9/20, 9/48, 9/68

(81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW.

(21) International Application Number: PCT/EP00/08857

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(22) International Filing Date:  
11 September 2000 (11.09.2000)

(25) Filing Language: English

Published:

- With international search report.
- Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.

(30) Priority Data:  
99118179.3 13 September 1999 (13.09.1999) EP

(88) Date of publication of the international search report:  
10 May 2001

(71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH];  
124, Grenzacherstrasse, CH-4070 Basle (CH).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(72) Inventors: DE SMIDT, Passchier, Christiaan; Benjamin de Tudela, 25-2B, E-31008 Pamplona (ES). HADVARY, Paul; Neumattenweg 8, CH-4105 Biel-Benken (CH). LENGSFELD, Hans; Marschalenstrasse 35, CH-4054 Basle (CH). SCHMID, Marcel; 2, Rebgasse, CH-4153 Reinach (CH). SMALL, David, MacFarland; 87 Harbourside Road, Quincy, MA 02171 (US). STEFFEN, Hans; 36, Fischmarkt, CH-4410 Liestal (CH). TARDIO, Joseph; 14, rue Petite Camargue, F-68300 St. Louis (FR).

(74) Agent: WITTE, Hubert; 124, Grenzacherstrasse,  
CH-4070 Basle (CH).

WO 01/19378 A3

(54) Title: SOLID LIPID FORMULATIONS COMPRISING AN INHIBITOR OF LIPASES AND A FATTY ACID ESTER OF POLYOLS

(57) Abstract: The present invention refers to a pharmaceutical composition comprising at least one inhibitor of lipases and at least one fatty acid ester of polyols, characterized in that the fatty acid ester has a melting point above the body temperature and the polyols

# INTERNATIONAL SEARCH REPORT

Inte onal Application No  
PCT/EP 00/08857

**A. CLASSIFICATION OF SUBJECT MATTER**  
**IPC 7 A61K9/20 A61K9/48 A61K9/68**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
**IPC 7 A61K**

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, MEDLINE, EMBASE**

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 34607 A (HOFFMANN LA ROCHE) 13 August 1998 (1998-08-13) page 6 -page 8; examples 1,2 page 8 -page 9; example 3 — US 5 741 496 A (KHAIAT ALAIN) 21 April 1998 (1998-04-21) column 2, line 20 - line 65 column 3, line 32 -column 4, line 19 — WO 00 09123 A (HOFFMANN LA ROCHE) 24 February 2000 (2000-02-24) cited in the application page 9 -page 10; examples 9,10 —	1,2,4-9, 14,18-27  1-6, 13-16, 20,22-27  1,4-7, 13-15, 17-27
P,X		

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

**2 March 2001**

Date of mailing of the international search report

**15/03/2001**

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl

Authorized officer

**Miller**

# INTERNATIONAL SEARCH REPORT

## Information on patent family members

Int'l	Application No
PCT/EP 00/08857	

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9834607	A 13-08-1998	US 6004996 A		21-12-1999
		AU 713192 B		25-11-1999
		AU 6097298 A		26-08-1998
		CA 2258095 A		13-08-1998
		CN 1220600 A		23-06-1999
		CN 1220600 T		23-06-1999
		CZ 9803528 A		17-02-1999
		EP 0921796 A		16-06-1999
		HR 980057 A		31-12-1998
		NO 985337 A		16-11-1998
		PL 330972 A		21-06-1999
		ZA 9800746 A		05-08-1998
		HU 0001468 A		28-09-2000
		JP 3059149 B		04-07-2000
		JP 11255645 A		21-09-1999
US 5741496	A 21-04-1998	FR 2710264 A		31-03-1995
		AT 186834 T		15-12-1999
		BR 9403783 A		23-05-1995
		CA 2132369 A,C		22-03-1995
		CN 1109740 A		11-10-1995
		DE 69421778 D		30-12-1999
		DE 69421778 T		21-06-2000
		EP 0643960 A		22-03-1995
		ES 2141208 T		16-03-2000
		GR 3032673 T		30-06-2000
		JP 7196469 A		01-08-1995
		PT 643960 T		28-04-2000
WO 0009123	A 24-02-2000	AU 5420599 A		06-03-2000
		US 6030953 A		29-02-2000

**THIS PAGE BLANK (USPTO)**